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Declining Tuberculosis Incidence Among People Receiving HIV Care and Treatment Services in East Africa, 2007–2012

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Background: Antiretroviral therapy (ART) reduces the risk of Tuberculosis (TB) among people living with HIV (PLWH). With ART scale-up in sub-Saharan Africa over the past decade, incidence of TB among PLWH engaged in HIV care is predicted to decline.

Methods: We conducted a retrospective analysis of routine clinical data from 168,330 PLWH receiving care at 35 facilities in Kenya, Tanzania, and Uganda during 2003–2012, participating in the East African region of the International Epidemiologic Databases to Evaluate AIDS. Temporal trends in facility-based annual TB incidence rates (per 100,000 person years) among PLWH and country-specific standardized TB incidence ratios using annual population-level TB incidence data from the World Health Organization were computed between 2007 and 2012. We examined

patient-level and facility-level factors associated with incident TB using multivariable Cox models.

Results: Overall, TB incidence rates among PLWH in care declined 5-fold between 2007 and 2012 from 5960 to 985 per 100,000 person years [$P = 0.0003$] (Kenya: 7552 to 1115 [$P = 0.0007$]; Tanzania: 7153 to 635 [$P = 0.0025$]; Uganda: 3204 to 242 [$P = 0.018$]). Standardized TB incidence ratios significantly decreased in the 3 countries, indicating a narrowing gap between incidence rates among PLWH and the general population. We observed lower hazards of incident TB among PLWH on ART and/or isoniazid preventive therapy and receiving care in facilities offering TB treatment onsite.

Conclusions: Annual TB incidence rates among PLWH significantly declined during ART scale-up but remained higher than the general population. Increasing access to ART and isoniazid preventive therapy and co-location of HIV and TB treatment may further reduce TB incidence among PLWH.

Key Words: TB incidence rates, tuberculosis, TB/HIV, HIV, ART, sub-Saharan Africa

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INTRODUCTION

Tuberculosis (TB) is the most common opportunistic infection among people living with HIV (PLWH) and the leading cause of death in PLWH globally.¹ Between 1990 and 2000, HIV-associated TB drove increasing TB incidence trends in sub-Saharan Africa,² although rates stabilized or declined elsewhere.³ In 2000, Jones et al⁴ found that antiretroviral therapy (ART) was highly effective in reducing the risk of TB disease in a US-based cohort. Subsequently, 8 PLWH cohorts from diverse settings, including sub-Saharan Africa,^{4–13} reported an average decline of 67% (95% Confidence Interval (CI): 61% to 73%) in the risk of TB associated with ART over an average 2-year follow-up.^{14,15} Meanwhile, ART coverage among all PLWH increased rapidly in sub-Saharan Africa since 2005 from single digits to 39% in 2014.¹⁶ Mathematical models have since then shown declining HIV-associated TB during the past decade in sub-Saharan Africa.^{17,18} These models included expanding ART coverage along with TB notification rates and baseline CD4 counts of

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PLWH as parameters. A few empirical studies have found declining case notification rates coinciding with ART scale-up.^{19,20} In addition, a recent study in Kenya found that during 2007–2012, estimated TB incidence declined by 28%–44% among PLWH—including those who are engaged and not engaged in HIV care—concurrent with an increase in ART uptake.²¹ To date, no study has examined temporal trends in facility-based annual TB incidence rates among PLWH engaged in HIV care over a period of rapid ART scale-up in sub-Saharan Africa. Furthermore, although a number of patient factors associated with incident TB disease among PLWH have been described,^{4,6–8,22–26} there are little data on the potential influence of facility-level factors, such as type and location of the facility, availability, and co-location of integrated TB/HIV services.

We used clinical data collected from 2003–2012 within the East African region of the International epidemiologic Databases to Evaluate AIDS (IeDEA) to determine temporal trends in facility-based annual TB incidence rates among PLWH in HIV care at predominantly public health facilities serving urban and semiurban population and to assess patient-level and facility-level factors associated with incident TB.

METHODS

Study Design

This is a retrospective study using data collected during routine clinical encounters from the East Africa IeDEA Cohort. The study period varied according to the country: January 2003 to December 2012 in Kenya and Uganda, and January 2006 to December 2012 in Tanzania. This study was approved by Moi Teaching and Referral Hospital/Moi University Institutional Research and Ethics Committee, Mbarara University of Science and Technology Institutional Review Committee, Uganda National Council for Science and Technology, St. Raphael of St. Francis Hospital Institutional Review Ethics Committee, Makerere University School Medicine Research & Ethics Committee, The United Republic of Tanzania Medical Research Coordinating Committee of the National Institute for Medical Research, Kenya Medical Research Institute/National Ethics Review Committee. Written consent was waived by the IRB because of the transmission of only deidentified data disseminated from the Regional Data Coordinating Center (RDC).

Study Setting

Eight programs representing 35 health facilities contributed data for analysis.²⁷

Study Population

PLWH who were ≥ 18 years of age, ART-naïve, and TB-disease-free at HIV care enrollment were included. PLWH with TB at enrollment or who initiated anti-TB treatment within 60 days of enrollment (25,300 patients) were excluded as possible prevalent cases.

Data Collection and Management

Data were collected using clinic-specific standard data collection forms and entered into patient-level databases locally. Prospective data quality controls to optimize accuracy and reduce missing data were incorporated into all data collection systems using methods for reconciliation of errors and retrieval of missing information from clinicians and primary records. At every site, periodic audits were conducted by the East African IeDEA RDC (Indiana University and Moi University) to identify errors, review data collection or entry procedures and investigate missing data. Data from all sites were harmonized at the RDC. Facility-level data were collected using an IeDEA facility survey.²⁸

Analysis

The outcome of interest was the first incident TB diagnosis, defined as first documentation of anti-TB medications within the patient record at least 2 months after enrollment into HIV care. Subsequent TB episodes were not included. TB diagnosis and subsequent initiation of treatment were largely based on clinical evaluation and smear microscopy during the period of this analysis.

Annual crude TB incidence rates [per 100,000 person years (PYs)] were estimated stratified by ART status (pre-ART or on ART), and age group (18–19, 20–29, 30–39, 40–49, 50+ years of age). We restricted the period of the trend analysis to 2007–2012 because estimates for the years before 2007 were unstable because of limited person time on follow-up. Time-updated ART status was used to account for different levels of risk during the pre-ART and ART phase. The annual crude TB incidence rates were divided by annual TB incidence rates (per 100,000 population per year) for the general population estimated by the World Health Organization (WHO), to derive country-specific standardized TB incidence ratios (SIRs)²⁹ for PLWH enrolled in HIV care at study sites. SIRs represent the relative likelihood that HIV patients in care would develop TB disease, as compared to the general population in the same country in a given year. To assess temporal trends in crude incidence rates and SIRs, linear regression was used.³⁰

We fitted adjusted Cox proportional-hazard models to 138,394 (82% of 168,330) PLWH with available data on all patient and facility variables, including imputed CD4 cell count and WHO stage, to examine the temporal trend in TB incidence after adjusting for patient-level and facility-level factors. Patient-level factors considered in adjusted analyses were age at enrollment, sex, enrollment year, WHO stage, CD4 cell count at enrollment, time-dependent ART use, history of TB disease before enrollment and use of isoniazid preventive therapy (IPT) at any time during HIV care. Facility-level factors included type of population served (rural, semi-urban, or urban), facility type (public, private, or other), availability of anti-TB treatment onsite, availability of routine TB screening based on a symptom checklist, and availability of IPT at the HIV clinic. We also assessed criteria for Cotrimoxazole preventive therapy (CPT) eligibility

TABLE 1. Clinical Characteristics of Patients Enrolling in HIV Care in 35 Facilities Participating in leDEA-East Africa, 2003–2012

	Kenya	Tanzania	Uganda	Overall
Number of patients	111,556	13,392	43,382	168,330
Age at enrolment				
Median, IQR	34.5 (28.2–42.2)	35.3 (29.5–42.5)	33.3 (38.0–40.1)	34.3 (28.2–41.5)
Missing	355	2	22	379
Sex				
Female	77,953 (69.9)	9635 (71.9)	28,303 (65.2)	115,891 (68.6)
Male	33,603 (30.1)	3757 (28.1)	15,079 (34.8)	52,439 (31.2)
Enrolment year				
2003	1256 (1.1)	NA	2693 (6.2)	3949 (2.3)
2004	4574 (4.1)	NA	5322 (12.3)	9896 (5.9)
2005	9488 (8.5)	NA	8038 (18.5)	17,526 (10.4)
2006	14,297 (12.8)	1949 (14.6)	5795 (13.4)	22,041 (13.1)
2007	16,358 (14.7)	2696 (20.1)	3981 (9.2)	23,035 (13.7)
2008	14,386 (12.9)	2810 (21.0)	4535 (10.5)	21,731 (12.9)
2009	16,366 (14.7)	1864 (13.9)	4195 (9.7)	22,425 (13.3)
2010	15,233 (13.7)	1706 (12.7)	5106 (11.8)	22,045 (13.1)
2011	13,465 (12.1)	1482 (11.1)	2918 (6.7)	17,865 (10.6)
2012	6133 (5.5)	885 (6.6)	799 (1.8)	7817 (4.6)
Follow-up time (mo)				
Median, IQR	42.1 (20.3–67.2)	44.6 (21.9–59.9)	50 (19.9–71.3)	44 (20.3–67.9)
Pre-ART	31.2 (12.0–56.8)	29.3 (11.1–49.9)	37.2 (12.0–62.4)	32.6 (12.0–58.6)
ART	46.7 (25.0–69.6)	48.8 (29.5–62.1)	56 (27.2–74.5)	49 (25.7–70.3)
CD4 ⁺ cells/μL at enrollment				
Median, IQR	280 (137–457)	261 (115–410)	297 (138–475)	283 (135–457)
0–99	20,437 (18.3)	2880 (21.5)	7541 (17.4)	30,858 (18.3)
100–199	21,068 (18.9)	2652 (19.8)	7269 (16.8)	30,989 (18.4)
200–350	25,758 (23.1)	2859 (21.4)	10,051 (23.2)	38,668 (23.0)
351–500	22,884 (20.5)	3186 (23.8)	9800 (22.6)	35,870 (21.3)
>500	21,297 (19.1)	1809 (13.5)	8716 (20.1)	31,822 (18.9)
Missing	112	6	5	123
WHO stage at enrollment				
Stage 1	54,836 (49.2)	3869 (28.9)	11,511 (26.5)	70,216 (41.7)
Stage 2	23,925 (21.5)	4854 (36.2)	16,342 (37.7)	45,121 (26.8)
Stage 3	28,523 (25.6)	3340 (24.9)	10,886 (25.1)	42,749 (25.4)
Stage 4	4192 (3.8)	1329 (9.9)	4642 (10.7)	10,163 (6.0)
Missing	80	0	1	81
Use of ART				
Yes	66,612 (59.7)	6450 (48.2)	19,390 (44.7)	92,452 (54.9)
No	44,944 (40.3)	6942 (51.8)	23,992 (55.3)	75,878 (45.1)
2003	419 (33.4)	—	436 (16.2)	855 (21.7)
2004	2363 (42.6)	—	1403 (20.1)	3766 (30.1)
2005	6976 (50.0)	—	4432 (35.3)	11,408 (43.0)
2006	12,790 (51.1)	786 (40.3)	5468 (39.0)	19,044 (46.4)
2007	17,943 (50.3)	1767 (46.5)	7084 (49.7)	26,794 (49.9)
2008	22,629 (53.6)	2511 (49.2)	8616 (54.3)	33,756 (53.4)
2009	29,710 (59.6)	2848 (57.3)	9845 (58.2)	42,403 (59.1)
2010	36,326 (65.6)	3082 (62.8)	11,250 (59.5)	50,658 (63.9)
2011	41,759 (72.0)	3106 (64.6)	12,117 (67.0)	56,982 (70.4)
2012	38,979 (78.1)	3102 (72.6)	5740 (75.4)	47,821 (77.4)
Use of isoniazid preventive therapy				
Yes	21,436 (19.2)	52 (0.4)	216 (0.5)	21,704 (12.9)
No	90,120 (80.8)	12,740 (99.6)	20,278 (99.5)	123,138 (87.1)
Missing	0	600	22,888	23,488
History of TB				

TABLE 1. (Continued) Clinical Characteristics of Patients Enrolling in HIV Care in 35 Facilities Participating in leDEA-East Africa, 2003–2012

	Kenya	Tanzania	Uganda	Overall
Yes	5308 (4.8)	NA	118 (0.3)	5426 (3.2)
No	106,248 (95.2)	NA	6281 (99.7)	112,529 (96.8)
Missing	0	13,392	36,983	50,375

Data is presented as n(%).

against 2006 WHO guidelines³¹ (eligibility criteria of CD4 cell counts either <350 or <500 cells per microliter as fully consistent; CD4 counts <200 cells per microliter or WHO stage III or IV as partially consistent).

Age and year of enrollment were treated as continuous variables. All other factors were treated as categorical variables. Records were censored at the date of the event or the last clinic visit for individuals identified as dead, lost to follow-up (LTFU), or transferred out. LTFU was defined as no visits for 6 months (for patients on ART) and 12 months (for pre-ART patients) without documentation of death or transfer. Patient-level and facility-level factors that were significant at the $\alpha = 0.20$ level in unadjusted analyses were included into the adjusted model. In the adjusted model, statistical significance was determined at the $\alpha = 0.05$ level. History of TB disease before enrollment was not available for the Tanzanian clinics and thus excluded from the adjusted model. We used robust standard errors to account for within-individual correlation resulting from treating ART as a time-dependent variable.

To examine the robustness of findings, we compared results including PLWH with imputed values for CD4 cell count and WHO stage at enrollment with results excluding them. Additionally, we ran country-specific models to examine whether observed associations in the multicountry model was driven by a single country. Statistical analyses were conducted in Stata version 10.0 (College station, TX).

Multiple imputation techniques were used to impute CD4 cell count for 23% and WHO stage for 12% of patients with missing data at enrollment based on a country-specific algorithm adapted from Yiannoutsos et al³² using WHO stage at enrollment if available to impute CD4 cell count and CD4 cell count if available to impute WHO stage, as well as age group, sex, and time from enrollment to ART start for ART patients for both measures.

RESULTS

Patient and Clinic Characteristics

Overall 168,330 adult PLWH enrolled in HIV care between 2003 and 2012 with a median follow-up time of 44 months [interquartile range (IQR): 20.3–67.9] (Table 1). Most patients were women (69%) with a median age of 34 (IQR: 28–42). Median CD4 cell count at enrollment was 283 cells per microliter (IQR: 135–457 cells per microliter) with little variability across countries. Approximately, one-third of

patients were enrolled with a WHO stage of III/IV disease. The proportion of patients with documented history of TB at enrollment ranged from 0.3% in Uganda to 5% in Kenya. IPT use was significantly higher in Kenya (19%) when compared with that in Tanzania and Uganda (<1%).

The proportion of PLWH initiating ART in any given year increased from 22% in 2003 to 77% in 2012. In Kenya, 60% of enrolled patients had initiated ART during the observation period compared to 48% in Tanzania and 45% in Uganda. 57% of patients were LTFU while in pre-ART care and 26% after ART initiation and 6% were known to have died.

TABLE 2. Clinic Characteristics of leDEA-East Africa Health Facilities, 2009

	Kenya	Tanzania	Uganda	Overall
Number of health facilities	27	3	5	35
Population served by facility				
Urban only	8 (30)	2 (67)	4 (80)	14 (40)
Rural only	5 (19)	0 (0)	0 (0)	5 (14)
Semiurban only	10 (37)	0 (0)	0 (0)	10 (29)
Urban and semiurban	4 (15)	1 (33)	0 (0)	5 (14)
Rural and semiurban	0 (0)	0 (0)	1 (20)	1 (3)
Facility type				
Public	24 (89)	3 (100)	4 (80)	31 (89)
Private/other	3 (11)	0 (0)	1 (20)	4 (11)
Availability of TB treatment within facility				
Yes	18 (67)	1 (33)	3 (60)	22 (63)
No	9 (33)	2 (67)	2 (40)	13 (37)
Routine TB screening at the HIV clinic				
Yes	25 (93)	2 (67)	5 (100)	32 (91)
No	2 (7)	1 (33)	0 (0)	3 (9)
Availability of isoniazid preventive therapy at the HIV clinic				
Yes	19 (70)	0 (0)	1 (20)	20 (57)
No	8 (30)	3 (100)	4 (80)	15 (43)
Consistency with WHO guidelines for Cotrimoxazole among PLWH				
Fully consistent	9 (33)	2 (67)	3 (60)	14 (40)
Partially consistent	18 (67)	1 (33)	2 (40)	21 (60)

Data is presented as n(%).

Patients received care in 35 health facilities (27 in Kenya, 3 in Tanzania, and 5 in Uganda). Most facilities served urban and semiurban populations (Table 2). Eighty nine percentage were public-sector facilities, 63% offered anti-TB treatment onsite, and 91% reported routine symptom-based TB screening. Onsite IPT availability was variable across countries, Kenya reported availability in 70%, Uganda in 20%, and Tanzania in no facilities. Consistency with WHO CPT guidelines was reported at 33%, 67%, and 60% of the facilities in Kenya, Tanzania, and Uganda, respectively.

Overall and Temporal Trends in TB Incidence

Between 2003 and 2012, 12,967 incident cases of TB were identified, 5471 during pre-ART and 7496 during ART period (Table 3). The overall 10-year crude TB incidence rate was 3986 per 100,000 PYs. Higher rates were reported in PLWH from Kenyan and Ugandan sites (4056 and 4138 per 100,000 PYs, respectively) compared to Tanzania (2321 per 100,000 PYs). In Uganda, TB incidence rates were highest among patients aged 18–19 years old and steadily declined with age. Across the 3 countries, the lowest TB incidence rates were found among the 50+ age group.

Crude TB incidence rates declined from 5960 to 981 per 100,000 PYs between 2007 and 2012 (coef. = -1889; $P = 0.0003$) (Table 3). The reduction in incidence was seen in all 3 countries [Kenya: from 7552 to 1115 (coef. = -2067; $P = 0.0007$); Tanzania: 7153 to 635 (coef. = -1253; $P = 0.0025$); Uganda: 3204 to 242 (coef. = -2017; $P = 0.018$)] (Fig. 1, Table 3). The declining trends were evident across pre-ART (coef. = -1487; $P = 0.0002$) and ART patients (coef. = -3290; $P = 0.0004$) and across all age groups, except the 18–19 age group for Uganda (Fig. 2).

TB Incidence Among PLWH Compared to the General Population

SIRs showed similar trends from 2007 to 2012 [Kenya: 21.8 to 4.1 ($P = 0.0019$); Tanzania: 53.4 to 3.1 ($P = 0.0022$); and Uganda: 12.2 to 1.4 ($P = 0.0404$)], indicating substantial decreases in TB incidence among PLWH engaged in HIV care relative to the general population (Table 3). Despite this decrease over the study period, enrolled PLWH continued to have a 1.4–4.1 times higher TB incidence than the general population.

Adjusted Analysis of Temporal Trends in TB Incidence

In the adjusted analysis, more recent year was associated with a lower hazard of TB disease. Other lower hazards of TB were increasing age, enrollment CD4 cell count between 100 and 199 cells per microliter and > 350 cells per microliter (vs. < 100 cells/ μ L), use of ART and IPT and receiving care at facilities with both HIV and anti-TB treatment available onsite. Factors associated with higher hazards of TB included male sex and WHO stage II, III and IV (vs. WHO stage I) at enrollment; receiving care in public health facilities (vs.

TABLE 3. Crude TB Incidence Rates and Standardized Incidence Ratios Among HIV Positive Individuals Enrolling in HIV Care in leDEA-East Africa Health Facilities, January 2003–December 2012

	Kenya	Tanzania	Uganda	Overall
Number of patients	111,556	13,392	43,382	168,330
Number of incident TB cases				
All	9149	396	3422	12,967
Pre-ART	3430	136	1905	5471
ART	5719	260	1517	7496
Person months of follow-up				
All	225,554	17,064	82,690	325,308
Pre-ART	84,218	5957	37,248	127,424
ART	141,335	11,107	45,442	197,883
TB incidence (per 100,000 PYs)				
All	4056	2321	4138	3986
ART status				
Pre-ART	4073	2283	5114	4294
ART	4046	2341	3338	3788
Age group				
18–19	4089	0	5658	4285
20–29	4167	2124	4514	4166
30–39	4178	2193	4372	4118
40–49	3865	2396	3574	3703
50+	3824	2010	3213	3585
Calendar year*				
2003	46,568	—	27,332	36,666
2004	20,686	—	7721	12,601
2005	13,708	—	25,820	19,787
2006	9263	8711	10,775	9888
2007	7552	7153	3204	5960
2008	5242	4878	3041	4604
2009	5124	2749	3234	4475
2010	3758	2090	2407	3332
2011	2950	1348	1208	2367
2012	1115	635	242	981
Standardized TB incidence ratio*†				
2003	133.4	—	78.1	—
2004	57.9	—	23.7	—
2005	38.2	—	84.9	—
2006	26.1	43.6	38.1	—
2007	21.8	53.4	12.2	—
2008	15.8	28.9	12.5	—
2009	16.4	17.8	14.3	—
2010	12.6	13.2	11.5	—
2011	10.2	8.4	5.3	—
2012	4.1	3.1	1.4	—

*Italicized rates are not included in calculations of trend statistics.

†Standardized TB incidence ratios = Rate ratio of TB incidence of PLWH in care over TB incidence of general population.

private facilities), facilities not exclusively serving an urban population (vs. urban population only), and facilities with routine symptom-based TB screening (Table 4).

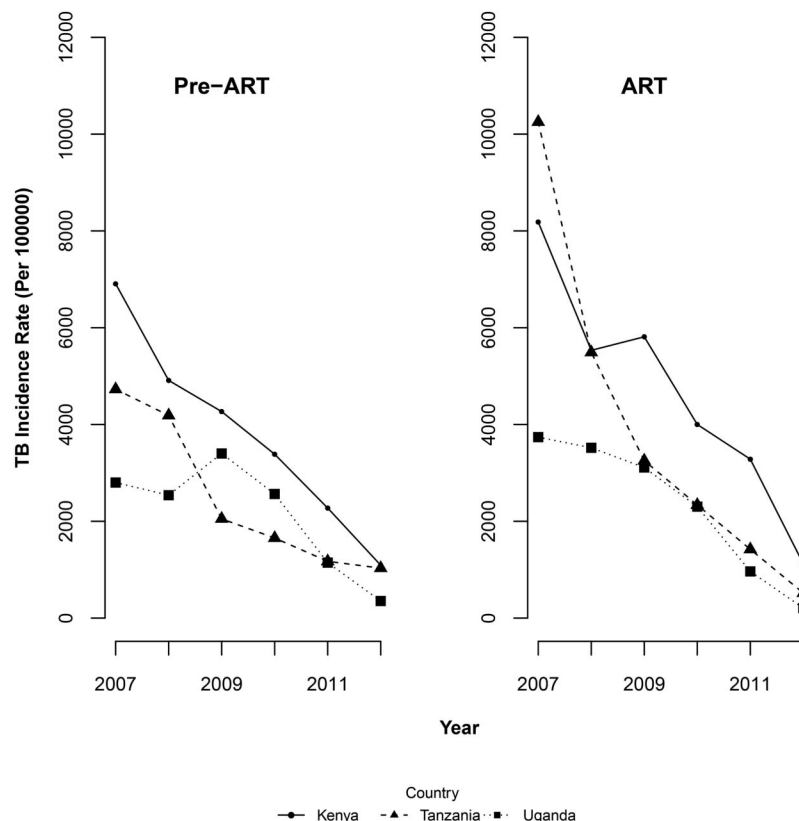


FIGURE 1. Trends in crude TB incidence rates among HIV-positive individuals enrolling in HIV care in 35 facilities participating in leDEA East Africa, January 2007–December 2012. Rates for 2003 for Kenya and Uganda and 2006 for Tanzania are not shown due to sparse cells.

In sensitivity analyses excluding observations with imputed values for CD4 cell count and WHO stage, we found higher TB incidence among those with missing CD4 cell count and/or WHO stage values. Those with missing values had an overall incidence rate of 4477 per 100,000 PYs compared with those without missing values that had an overall incidence rate of 3868 per 100,000 PYs. This is likely because they were less likely to be on ART (35.9% vs. 62.5%) and on IPT (7.9% vs. 17.7%). Model results excluding imputed values for CD4 cell count and the WHO stage, however, yielded consistent results with those using imputed data with minor variation in point estimates and *P*-values, which indicated no significant differences in factors associated with incident TB between the 2 groups. Additionally, we ran country-specific models and found that more recent enrollment years were associated with lower hazard ratio for TB in all models. Although we found broad consistency in the direction of association with patient-level and facility-level factors with incident TB, we found important differences in a few variables. At the individual level, IPT use was significantly associated with decreased risk of TB in Kenya, not associated in Tanzania, and associated with increased risk in Uganda. Paradoxically, at the facility level, availability of IPT at the HIV clinic was significantly associated with a higher risk of TB in Kenya, whereas the opposite was true in Uganda. In Tanzania, the variable dropped out of the model because of collinearity. Finally, public clinic was associated with lower risk of incident TB in

Kenya, whereas it was associated with higher risk of incident TB in Uganda.

DISCUSSION

Among 168,330 PLWH receiving HIV care at 35 clinics in Kenya, Tanzania, and Uganda, we found a 5-fold decline in TB disease incidence from 2007 to 2012 the period of ART scale-up in which ART coverage among all PLWH increased from 14% to 46%, 9% to 29%, and 11% to 32%, in Kenya, Tanzania, and Uganda, respectively.³³ The significant declining trend, moreover, was still present after adjustment for confounding in the multivariate model. The magnitude of the decline was greater than modeling estimates of HIV-associated TB incidence.^{17,18} The WHO Global TB Report of 2014, for example, found a 66%, 110% and 82% decline in Kenya, Uganda, and Tanzania, respectively, between 2004 and 2013.¹⁷ These estimates, however, are for all PLWH regardless of whether or not they are engaged in HIV care. A study in a periurban township in South Africa, conversely, found a 1.7-fold decrease in case of notification among PLWH on ART between 2004 and 2008—a larger decline than modeling studies.¹⁹ Accounting for the shorter observation period of that study compared with that of this study, the magnitude of decline observed in our facilities was still higher.

Findings from this large multicountry study demonstrate significant decreases in annual TB incidence coinciding

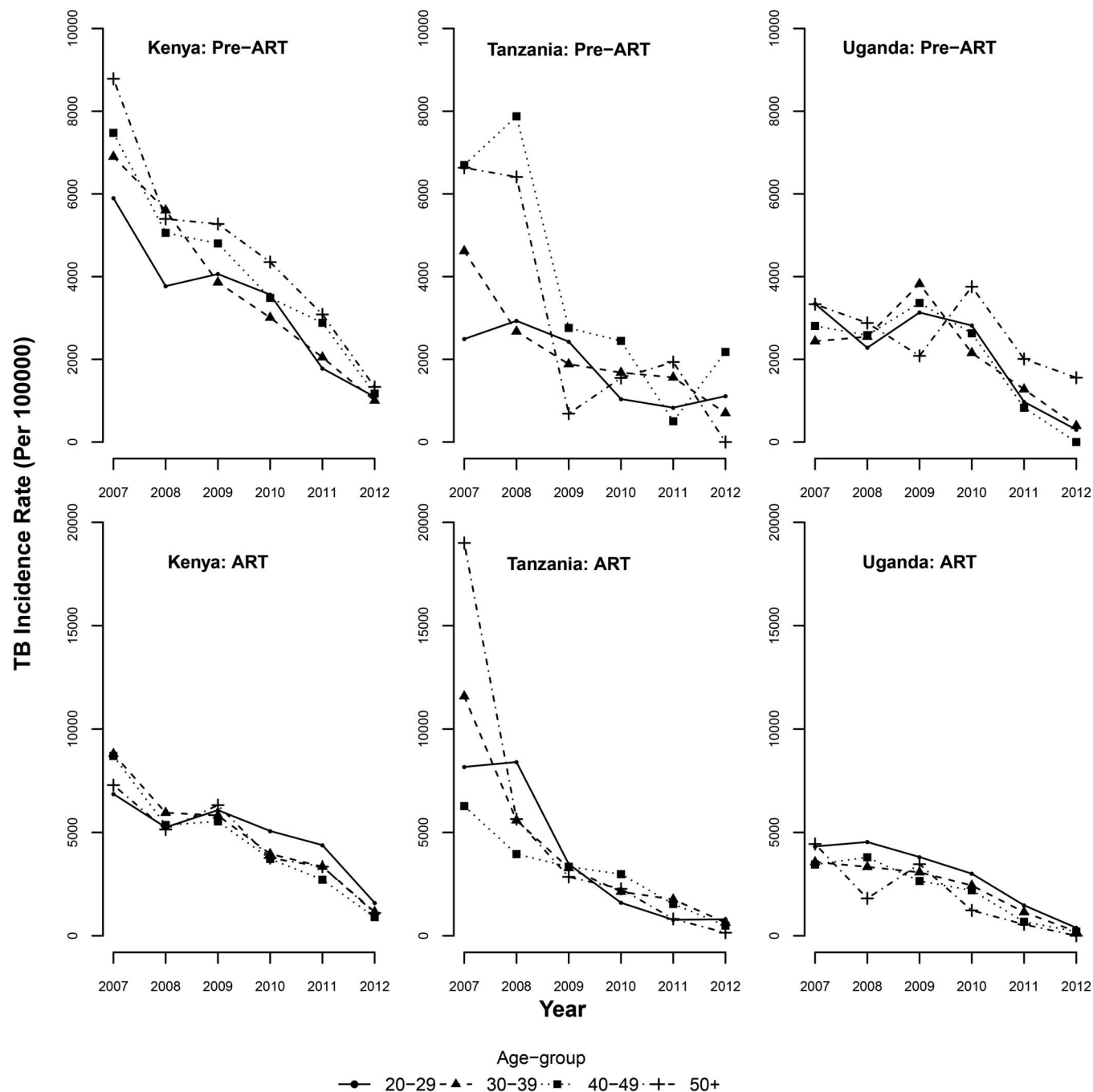


FIGURE 2. Trends in crude TB incidence rates among HIV-positive individuals enrolling in HIV care in 35 facilities participating in IeDEA-East Africa, by age group and by ART status, January 2007–December 2012. Rates for patients 18–19 are not shown due to sparse cells.

with a decade-long scale-up of ART services, mirroring studies of single cohorts examining the ART effectiveness in reducing TB incidence.^{4–13} We found declining TB incidence in pre-ART and ART patients. The decline in pre-ART care could partially be explained by reduced transmission of TB both in the community and in the facility because of ART scale-up, despite predictions of low effect.³⁴ IPT scale-up among PLWH may also contribute.¹⁷ We found

a 33% protective effect of IPT against incident TB. Finally, the decline may, in part, be an artifact of the very high incidence of TB among PLWH engaged in care in Kenya in 2004 and Uganda in 2005. These rates may be a function of either the early effects of HIV epidemic on increased progression to TB disease in those infected or of active case finding in HIV centers or both. A similar phenomenon was observed in Peru during its initial years of active TB control.³⁵

TABLE 4. Unadjusted and Adjusted Hazard Ratios for Patient and Facility-Level Factors Associated With Incident TB Among Patients Enrolling in HIV Care in leDEA East Africa Health Facilities, 2003–2012 (n = 138,394)

	HR	95% CI	P	aHR	95% CI	P
Patient-level factors						
Age at enrollment	1.004	(1.002 to 1.006)	<0.001	0.996	(0.994 to 0.998)	<0.001
Sex						
Male	1.447	(1.394 to 1.504)	<0.001	1.314	(1.263 to 1.368)	<0.001
Female	1.000			1.000		
Enrollment year	0.924	(0.916 to 0.933)	<0.001	0.948	(0.938 to 0.958)	<0.001
CD4 ⁺ cells/ μ L at enrolment						
0–99	1.000			1.000		
100–199	0.824	(0.781 to 0.869)	<0.001	0.911	(0.862 to 0.963)	0.001
200–350	0.806	(0.765 to 0.849)	<0.001	0.981	(0.925 to 1.040)	0.515
351–500	0.662	(0.625 to 0.701)	<0.001	0.837	(0.779 to 0.899)	<0.001
500+	0.440	(0.411 to 0.471)	<0.001	0.594	(0.547 to 0.645)	<0.001
WHO stage at enrolment						
Stage 1	1.000			1.000		
Stage 2	1.495	(1.425 to 1.568)	<0.001	1.412	(1.343 to 1.484)	<0.001
Stage 3	2.348	(2.245 to 2.456)	<0.001	2.097	(1.992 to 2.207)	<0.001
Stage 4	2.598	(2.403 to 2.809)	<0.001	2.240	(2.054 to 2.442)	<0.001
Use of ART						
Yes	1.168	(1.123 to 1.214)	<0.001	0.843	(0.798 to 0.891)	<0.001
No	1.000			1.000		
Use of IPT						
Yes	0.716	(0.684 to 0.750)	<0.001	0.767	(0.728 to 0.809)	<0.001
No	1.000			1.000		
History of TB*	1.622	(1.504 to 1.750)	<0.001			
Facility-level factors						
Facility type						
Public clinic	1.502	(1.312 to 1.719)	<0.001	1.392	(1.196 to 1.619)	<0.001
Private clinic	1.000			1.000		
Population served						
Urban	1.000			1.000		
Urban and semiurban	0.822	(0.791 to 0.854)	<0.001	0.956	(0.913 to 0.999)	0.049
Rural and semiurban	0.719	(0.663 to 0.780)	<0.001	0.788	(0.723 to 0.859)	0.000
Availability of TB treatment within facility	0.808	(0.778 to 0.839)	<0.001	0.932	(0.878 to 0.989)	0.021
Routine TB screening at the HIV clinic	1.364	(1.119 to 1.663)	0.002	1.260	(1.026 to 1.542)	0.027
Availability of IPT at the HIV clinic	0.889	(0.853 to 0.927)	<0.001	1.042	(0.868 to 1.243)	0.678
Consistency with WHO guidelines for Cotrimoxazole among PLWH	1.116	(1.071 to 1.162)	<0.001	0.894	(0.781 to 1.024)	0.106
Country						
Kenya	1.000			1.000		
Tanzania	0.508	(0.458 to 0.564)	<0.001	0.480	(0.407 to 0.565)	0.000
Uganda	1.501	(1.435 to 1.569)	<0.001	1.176	(1.030 to 1.343)	0.016

*Model includes only Kenya and Uganda, as Tanzania did not report this variable.
aHR, adjusted hazard ratio; HR, hazard ratio.

We also found that the SIRs decreased significantly, suggesting that the gap between TB incidence among PLWH in care and the general population narrowed over the study period. Despite previous recognition that general economic development with improved nutrition decreases TB incidence,^{36,37} the substantial decline in SIRs suggest that scale-up of HIV care contributed additional benefit in reduction of TB disease in PLWH in care as past studies have shown.^{19,21} Yuen et al, for example, found estimated TB incidence rates in Kenya among HIV-negative people

reduced approximately at half the rate of HIV-positive people (11%–26% vs. 28%–44% decline between 2007 and 2012).²¹ In our study, despite the greater decline in PLWH in care, TB incidence among them remained 1.4–4.1 times higher than in the general population at the end of the study period in all three countries. This finding is anticipated; ART does not return patients, particularly those with a very low CD4 count to a pre-HIV infection immune status.^{26,34,38}

Consistent with previous studies, use of ART and IPT was associated with a reduced incidence of TB.^{4,6–9,13,22,24} As

previously described, female sex,³⁹ higher CD4 cell count, and lower enrollment WHO stage were associated with lower hazard of TB.^{22,23} Although other studies and our unadjusted models found that increasing age was associated with a higher hazard of TB,^{13,24} once we adjusted for immunosuppression measures at enrollment this finding was reversed. In post hoc analyses we found that older PLWH had longer time on ART than younger PLWH, which may explain this finding because longer time on ART has been shown to reduce risk of TB.⁶

We also found important facility-level factors associated with incident TB. PLWH receiving care at public-sector facilities and in facilities serving only urban populations were more likely to have incident TB. The urban setting has been linked to higher rates of incident TB in previous studies, plausibly mediated by high population density and crowded living conditions.³⁶ PLWH receiving care at health facilities providing anti-TB treatment onsite were less likely to have incident TB. Integration of HIV and TB programs has been associated with high cure and treatment completion rates.^{40,41} Our study has found that it may also reduce incident TB among PLWH engaged in care, presumably by reducing TB transmission in the community by reducing treatment delays. Although IPT was significantly associated with reduced risk of incident TB, availability of IPT at the HIV clinic was not associated with reduction in incident TB. This may be explained by availability of IPT not always translating to patients actually receiving the treatment, a probability in Kenya where 80% of health facilities reported IPT availability but only 20% of patients had documentation that they received it.

Our study has some limitations. We had a substantial amount of missing data, most notably enrollment CD4 cell count and WHO stage. We used multiple imputation techniques to address CD4 data incompleteness in our analyses. However, if these data were not missing at random, the results based on the imputed data could be biased.⁴²

Although the proportion of patients LTFU in our study was comparable with that of other studies,^{43–45} attrition bias is possible if the likelihood of LTFU was associated with incident TB. Nevertheless, we do not believe that the significant decline in TB incidence found can be explained by greater LTFU by patients with incident TB, because rates of LTFU in our study population also declined over the study period from 58% to 19%.

In addition, we had missing observations resulting in the models for incident TB using only 82% of the total study population. However, because demographic and clinical characteristics of PLWH included in and excluded from the models were very similar to each other (data not shown), it is unlikely that model results are seriously biased.

Incident TB was defined as the first-documented initiation of anti-TB treatment. Use of anti-TB treatment initiation to define incident TB lends itself to misclassification biases in both directions. Diagnostic challenges remain especially in PLWH where smear negative and extrapulmonary TB are common; some patients are not diagnosed caused by these limitations and therefore not treated, whereas other patients are “overtreated” because of clinician’s fear of missing TB.

SIRs standardized the TB incidence rates of PLWH engaged in HIV care to the annual TB incidence rates (per

100,000 population per year) for the general population estimated by the World Health Organization (WHO). Our study population, however, was PLWH engaged in care predominantly in public health facilities serving urban and periurban areas. Because TB incidence is likely higher in urban areas, SIRs in this study could therefore be inflated.

Another possible limitation relates to the fact that facility-level factors were assessed in a 2009 survey and were assumed to be unchanged through the study period. It is likely that clinic practices for TB treatment within facility, routine TB screening at HIV clinic, availability of IPT at HIV clinic, and consistency with WHO guidelines for CPT among PLWH changed over time so that 2009 practices may not be representative of earlier or later practices. Such misclassifications would attenuate associations between health facility level factors and incident TB.

In addition, it is important to note that although most health facilities were public health facilities which are the backbone of the national HIV response in Kenya, Tanzania, and Uganda, they were not selected to be representative of the health facilities delivering HIV care in these countries. The vast majority of the health facilities (77%) and patients (66%) came from 3 regions in Kenya which represented 7% (38,979/548,588) of the reported number of adults receiving ART in Kenya in 2012.⁴⁶

Finally, there may be important country-level differences in factors associated with incident TB that we were not able to fully explore in this analysis. Our sensitivity analyses, for example, showed that IPT use at individual level was associated with higher risk of TB in Uganda. We believe, however, that this is an artifact of poor data quality for that variable in Uganda (53% missing).

Our study also has important strengths. With data on nearly 170,000 PLWH with 13,000 incident TB cases from 35 HIV care clinics in three countries with heterogeneous HIV epidemics, this study during early rapid ART scale-up is the largest assessment of HIV-related TB incidence in this region. Six years of observation for the temporal trend analysis allowed for examination of TB incidence over a critical period of scale-up of HIV treatment in East Africa. Using data routinely collected across countries increased the generalizability of study findings. Finally, we examined health facility-level factors associated with TB incidence that have not been previously examined.

In conclusion, we found a significant decline in TB incidence among patients in HIV care in Kenya, Tanzania, and Uganda between 2007 and 2012 coincident with the rapid scale-up of HIV treatment across the region. SIRs significantly decreased during in all 3 countries, indicating that the TB incident rate gap among PLWH in HIV care and that of the general population narrowed. These findings are encouraging, as efforts continue to improve access to and early initiation of ART, IPT, and TB/HIV care integration. Future studies must examine this causal impact of ART scale-up on reduction of TB incidence and mortality among PLWH. Minimizing TB remains of critical importance for continued and sustained success in reduction of morbidity and mortality in East Africa.

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